May 11, 2006
US Serial No. 09/835,537

REMARKS

Claims 19 and 21 - 35 are currently pending.

In the Office Action, the rejection of claims 19 and 21 – 35 under 35 USC §112, first paragraph, was maintained. This rejection is again respectfully traversed, as further explained and argued below.

First, the remarks in the Office Action indicate that Applicants previously argued in response to this rejection that 'guanidinoacetate' is not a salt, and is not the same as 'guanidine acetate'. Applicants wish to clarify the record. The basis for Applicants' argument was that the claims should not be deemed unacceptably broad under §112, because the rejection did not provide a reasonable basis for limiting 'guanidine salt' to only guanidine HCl. The issue of 'guanidinoacetate' vs. 'guanidine salt' was only raised in reference to the §102(e) and §103 rejections. It is believed that Applicants' previous argument adequately refutes the aspect of this rejection relating to the breadth of 'guanidine salts', and reconsideration of those remarks is respectfully requested.

Second, the comments in the instant Office Action concerning the breadth of prion diseases recited in the claims still fails to provide a sound basis for limiting the scope. Applicants, thus, reiterate their previous argument:

"The specification states at page 10, lines 16 – 18, that prion diseases are disorders associated or caused by the conversion of the cellular type of prion protein to the scrapie type of prion protein or its consequent aggregation. While the specification (and claim 23) mentions a number of the most important encephalopathies, it was not intended to be an exhaustive list. The burden is on the Patent Office to establish a reasonable basis for inferring that the treatment would not work on a prion disease other than those in claim 23, and without that the presumption of patentability lies in Applicants' favor."

There is nothing in the patent law that states that Applicant is only entitled to what is mentioned in working examples. In fact, examples themselves are not a required element for patentability. Without some sound, scientific reason for

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questioning the applicability of the invention to any prion disease, the Patent Office has not met its burden of establishing a case of overbreadth under §112.

For the reasons stated above, the scope of the invention as claimed, with respect to both "guanidine salts" and prion diseases, is fully enabled by the specification in light of the state of the art. Withdrawal of this rejection is therefore deemed proper.

The rejections of claims 19 and 22 – 29 under 35 USC §102(e) and of claim 30 under §103 over Kaddurah-Daouk et al. are again respectfully traversed.

The comments in the Office Action appear to indicate some confusion about the molecules 'guanidinoacetate' and 'guanidine salt'. In the previous response, Applicants stated that "...'guanidine acetate', ...may be recognized as a salt of guanidine...". In fact, Applicants are unaware if any such salt of guanidine exists. However, the statement was only intended to point out an apparent discrepancy in nomenclature, which is that *guanidinoacetate* is not equivalent (in chemical name) to *guanidine acetate*. To further illustrate the differences in the compound of Kaddurah-Daouk (guanidinoacetate) and a guanidine salt according to the present invention, attached to this paper (as Exhibit A) is a diagram showing the chemical structures of guanidine (showing also its ionic (base) form), and guanidinoacetate. Despite sharing the root "guanidin-", they are clearly different molecular entities. In fact, guanidinoacetate (GAA) is a salt or anionic form of *guanidinoacetic acid* (identical to the structure of guanidinoacetate shown, but with an H atom at the COO group). Structurally, the GAA contains an additional C atom and the acetyl molety as compared to guanidine. Moreover, chemically they are quite different, because guanidine is a strong base and GAA is an acid form. Exhibit A also contains a list of a number of commonly available guanidine salts and their structures. No mention of 'guanidine acetate' could be found in the literature.

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To further evidence the differences between the compounds, attached to this paper is portion of Dorland's Illustrated Medical Dictionary (Exhibit B – two pages), which gives the definitions of *guanidine* and *guanidinoacetate* (note asterisks), as well as a number of similarly named chemicals.

As the pending prior art rejection depends solely on the issue of whether GAA is a guanidine salt or not, the Examiner is respectfully requested to reconsider his position that "*Guanidinoacetate and guanidine acetate are equivalent compounds arising from a combination of guanidine and acetate.*" [emphasis added], especially in view of the information in the exhibits submitted herewith.

Applicants' position in view of the novelty rejection is that the cited art discloses a molecule that is not only chemically and structurally different from the guanidine salts of the present claims, but is also the very opposite in chemical nature (i.e., an acid vs. a base). Thus, the cited publication clearly does not teach the presently claimed invention. Accordingly, this rejection should be reconsidered and withdrawn.

Similarly, the rejection of claim 30 under 103(a) should be withdrawn, because the molecule disclosed in the Kaddurah-Daouk reference is not at all related to guanidine salts. In other words, one skilled in the art would not have been motivated in the least to substitute guanidinoacetate with a guanidine salt to arrive at the present invention.

Applicants respectfully submit that claims 19 and 21 – 35 are in condition for allowance. Especially given the protracted prosecution in this application (pending now for over five years), the Examiner is courteously requested to contact the undersigned at the number or email listed below should he believe there are any remaining issues that could be more expeditiously resolved by direct communication or by personal/telephone interview.

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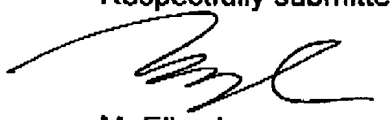
This paper is being submitted prior to the three-month period for response; therefore, no fee is due with this response.

Respectfully submitted,



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Enclosures: Exhibits A and B (3 pages)

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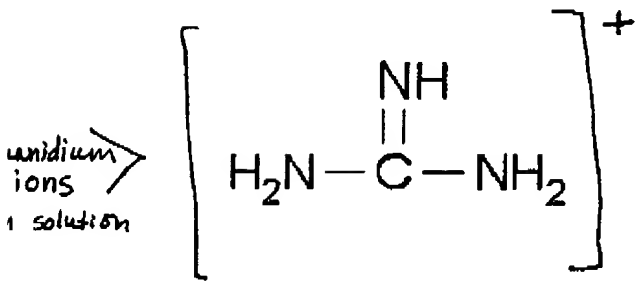
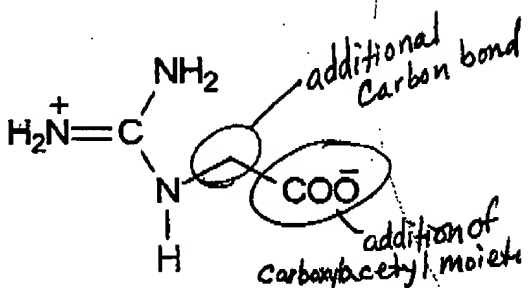
Guanidine (in solution is a strong base, favoring salt formation)

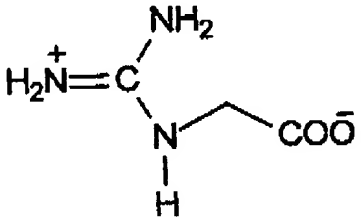


VS.



Guanidinoacetate (GAA)

Exhibit A



Guanidinoacetate (GAA)

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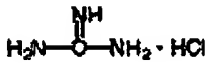
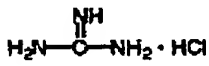
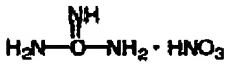
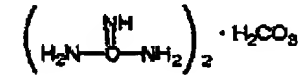
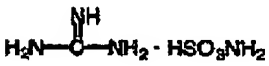
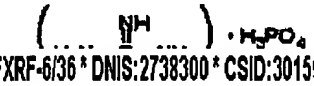
1. Guanidine salts for industry

Brand name	Structure
Guanidine hydrochloride (60% Aqueous Solution)	
Guanidine hydrochloride	
Guanidine nitrate	
Guanidine carbonate	
Guanidine sulfamate (APINON - 101)	
Guanidine phosphate (APINON - 303)	

(Page 1)

Exhibit B

MERCK SOURCE A world of health information at your fingertips.

Powered by Dorland's Illustrated Medical Dictionary

This information is provided by an independent source. Merck & Co., Inc. is not responsible for this content. Please discuss any and all treatment options with your healthcare professional. The manufacturer of a product generally has the most complete information about that product.

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guanethidine monosulfate (guan·eth·i·dine mo·no·sul·fate) (gwahn-eth'ĭ-dēn) [USP] an adrenergic neuron blocking agent used as an antihypertensive; administered orally.

guanfacine hydrochloride (guan·fa·cine hy·dro·chlo·ride) (gwahn'fe-sēn) [USP] an α_2-adrenergic agonist that stimulates the α_2-adrenergic receptors of the central nervous system, resulting in a reduction of sympathetic outflow to the heart and peripheral vascular system, used as an antihypertensive; administered orally.

* **guanidine (gua·ni·dine)** (gwah'nĭ-dēn) the compound $NH=C(NH_2)_2$, a strong base found in the urine as a normal product of protein metabolism. It is used in laboratory research as a protein denaturant.

g. phosphate a less correct term for *phosphoguanidine*.

* **guanidine-acetic acid (gua·ni·dine-acet·ic ac·id)** (gwah'nĭ-dēn-ə-se'tik) guanidinoacetic acid.

guanidinemia (gua·ni·din·emia) (gwah"nĭ-dĭ-ne'me-ə) the presence of guanidine in the blood.

(page 2)

(Exhibit B)

guanidinium (gua·ni·din·i·um) (gwah"nĭ-din´e-əm) the radical derived from guanidine; the guanidinium group is an important component of arginine and creatine.

guanidino (gua·ni·di·no) (gwah"nĭ-de´no) guanidinium.

* **guanidinoacetate (gua·ni·di·no·ac·e·tate)** (gwah"nĭ-de"no-as´ə-tāt) a salt or anionic form of guanidinoacetic acid.

guanidinoacetate *N*-methyltransferase (gua·ni·di·no·ac·e·tate *N*-meth·yl·trans·fer·ase) (gwah"nĭ-de"no-as´ə-tāt meth"əl-trans´fər-ās) [EC 2.1.1.2] a cytosolic enzyme of the transferase class that catalyzes the methylation of guanidinoacetate to form creatine, the final step in the biosynthesis of creatine. The methyl donor is *S*-adenosylmethionine, and the enzyme is concentrated in the kidney and pancreas.

* **guanidinoacetic acid (gua·ni·di·no·a·ce·tic ac·id)** (gwah"nĭ-de"no-ə-se´tik) a nitrogenous compound formed enzymatically in the liver, pancreas, and kidney by a reaction transfering an amidino group between arginine and glycine, and *N*-methylated in the liver by *S*-adenosylmethionine to form creatine. Called also *glycocyamine*, *guanidine-acetic acid*, and *guanido-acetic acid*.

guanido (gua·ni·do) (gwah´nĭ-do) guanidinium.

guanido-acetic acid (gua·ni·do-ace·tic ac·id) (gwah"nĭ-do-ə-se´tik) guanidinoacetic acid.

guanine (gua·nine) (gwah´nēn) a purine base, in animal and plant cells usually occurring condensed with ribose or deoxyribose to form the nucleosides guanosine and deoxyguanosine; these nucleosides are components of nucleic acids and of free nucleotides important in metabolism. Symbol G. See it also illustration at *purine base*, under *base*.

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